REMARKS

Claims 1-81 were pending. By virtue of this response, claims 1-9 and 60-80 are withdrawn from consideration; claims 19-21 and 40-57 are cancelled. Accordingly, claims 10-18, 22-39, 58, 59 and 81 are under consideration.

Claims 10 and 59 are directed to a method and a kit for measuring a physiological level of whole parathyroid hormone in a mammalian sample. An isolated antibody that specifically binds to an N-terminal sequence of whole PTH and is capable of detecting said whole PTH at a physiological level in said mammalian sample, but avoids binding to a non-whole PTH fragment is used in the method and kit. The phrase "avoids binding" is explained in the present specification:

> Antibodies or antibody fragments that avoid binding a particular moiety generally contain a specificity such that a large percentage of the particular moiety would not be bound by such antibodies or antibody fragments. This percentage generally lies within the acceptable cross reactivity percentage with interfering moieties of assays utilizing antibodies directed to detecting a specific target.

(*See* the present specification at page 14, paragraph **[0066]**.) Therefore, the purpose of using such an antibody is to avoid interfering moieties of assays, which interfering moieties to be avoided are necessarily the interfering moieties in the samples to be assayed. The amendment of claims 10 and 59 makes this clear and finds support in the present specification. Support for amended claim 17 can be found throughout the original application, and *inter alia*, in the original claim 17. Support for amended claim 22 can be found throughout the original application, and *inter alia*, in the original claim 22 and at page 17, paragraph **[0080]**. Claim 81 is amended to correct a spelling error.

The amendments are made solely to promote prosecution without prejudice or disclaimer of any previously claimed subject matter. With respect to all amendments and cancelled claims, Applicant has not dedicated or abandoned any unclaimed subject matter and moreover has not acquiesced to any rejections and/or objections made by the Patent Office. Applicant expressly reserves the right to pursue prosecution of any presently excluded subject matter or claim embodiments in one or more future continuation and/or divisional application(s).

Applicant has carefully considered the points raised in the Office Action and believes that the Examiner's concerns have been addressed as described herein, thereby placing this case into condition for allowance.

Election/Restrictions

The Examiner requests restriction of the present invention to one of the four groups:

I. Claims 1-9, drawn to an isolated antibody, classified in class 530, subclass 387.2.

II. Claims 10-18, 22-59, 81, drawn to a method for measuring whole parathyroid hormone in a mammalian sample, classified in class 435, subclass 7.1.

III. Claims 60-65, 72-74, 78-80, drawn to an isolated parathyroid hormone, classified in class 435, subclass 335.

IV. Claims 66-71, 75-77, drawn to a multiple antigenic peptide, classified in class 436, subclass 547.

Applicant has provisional elected Group II (Claims 10-18, 22-59 and 81) with traverse during a telephone conversation on October 18, 2004 between the Examiner and the undersigned. The Examiner requests affirmation of this election.

Applicant hereby elects Group II (Claims 10-18, 22-59 and 81) for continued examination.

Applicant expressly reserves the right under 35 U.S.C. § 121 to file a divisional application directed to the non-elected subject matter specified in claims 1-9 and 60-80 during the pendency of this application, or an application claiming priority from this application.

Double Patenting

Claims 10-18, 22-30, 58-59 are rejected under the judicially created doctrine of obviousness-type double patenting as being allegedly unpatentable over claim 5-26 of U.S. Patent No. 6,689,566 (the '566 Patent). The Examiner states that although the conflicting claims are not identical, they are not patentably distinct from each other because the antibody used in the instant application specifically binds to the N-terminal sequence of the whole PTH, while more broadly defined than the antibody used in the issued claimed method of the '566 Patent, nevertheless an ordinary skilled person in the art would have recognized that the limitation of the issued claimed antibody specific binds to the initial N-terminal of PTH (SEQ ID NO:3) would encompass the claimed subject matter of the instant application.

Applicant respectfully traverses this rejection. Claims 5-26 of the '566 Patent and presently pending claims, *e.g.*, claims 10 and 59, are directed to patentably distinct inventions. For example, the presently pending claims 10 and 59 require that the antibody be capable of detecting whole PTH at a physiological level in a mammalian sample to be tested and claims 5-26 of the '566 Patent have no such requirement. However, in order to advance prosecution, applicant will file a terminal disclaimer once allowable subject matter is indicated.

For all of the above reasons, Applicant respectfully requests withdrawal of the double patenting rejection.

Information Disclosure Statement

The Examiner states that the information disclosure statement filed 3/1/2004 fails to comply with the provisions of 37 CFR 1.97, 1.98 and MPEP § 609 because foreign document DE 3347548 (German) is not coupled with an English translation. The Examiner also states that document US 60/224396 (Hammis et al.) is not a patent under inventor. The Examiner further

states that these two documents have been placed in the application file, but the information referred to therein has not been considered as to the merits.

Enclosed herewith is an English abstract for DE 3347548 (Exhibit B). Also enclosed herewith is a copy of U.S. provisional patent application Serial No. 60/224,396, filed August 10, 2000 (Exhibit C). Mr. Cantor is the listed inventor for this application. Accordingly, applicants requests the Examiner to consider and make record of these two items in the present application.

Applicant will file a Supplemental Information Disclosure Statement shortly.

Rejections under 35 U.S.C. §112, first paragraph

Claims 40-57 are rejected under 35 U.S.C. 112, first paragraph, as allegedly failing to comply with the enablement requirement. The Examiner states that the claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Applicant respectfully traverses this rejection. However, in order to advance prosecution, claims 40-57 are canceled. Applicant reverses the rights to pursue the canceled subject matter in a subsequent application.

For all of the above reasons, Applicant respectfully requests withdrawal of all rejections under 35 U.S.C. 112, first paragraph.

Rejections under 35 U.S.C. §112, second paragraph

Claims 10-18, 22-59 and 81 are rejected under 35 U.S.C. 112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The Examiner states that with respect to claim 10, it is not clear whether the recited method requires a radiolabeled or fluroesence[sic] labeled antibody to detect the binding of the complex.

Applicant respectfully traverses this rejection. Claim 10 is directed to a method for measuring a physiological level of whole parathyroid hormone in a mammalian sample using, *inter alia*, an isolated antibody that specifically binds to an N-terminal sequence of whole PTH and is capable of detecting said whole PTH at a physiological level in said mammalian sample, with a proviso that said isolated antibody avoids binding to a non-whole PTH fragment in said sample. As long as an antibody with the requisite binding specificity is used, the method or assay can be conducted in any suitable format. For example, the present specification teaches:

> Although a variety of assay types are contemplated, the present methods frequently assess the complex formed between the whole parathyroid hormone and the antibody via a sandwich or competitive assay format. On occasion, the complex is assessed in a homogeneous or a heterogeneous assay format. Also frequently, the complex is assessed by a format selected from the group consisting of an enzyme-linked immunosorbent assay (ELISA), immunoblotting, immunoprecipitation, radioimmunoassay (RIA), immunostaining, latex agglutination, indirect hemagglutination assay (IHA), complement fixation, indirect immunofluorescent assay (IFA), nephelometry, flow cytometry assay, plasmon resonance assay, chemiluminescence assay, lateral flow immunoassay, u-capture assay, inhibition assay and avidity assay.

(*See* the present specification at pages 5-6, paragraph **[0019]**.) Radioactive or fluorescent label certainly can be used; but other labels, *e.g.*, enzyme or chemiluminescent label, can be used as well. In addition, depending on the assay formats, an antibody can be labeled as in a sandwich assay

format. But in other formats, *e.g.*, a competitive assay format, a label can be attached to an analyte or analyte analog.

The Examiner states that with respect to claim 10, step (c), "assessing a complex formed" is allegedly vague and indefinite. The Examiner asserts that it is not clear what step(s) constitutes "assessing." The Examiner also asserts that it is not clear whether this "assessing" step directly relates to the measurement of the level of the whole PTH.

Applicant respectfully traverses this rejection. Step (c) of claim 10 recites "assessing a complex formed between said whole parathyroid hormone, if present in said sample, and said antibody." As discussed above, as long as an antibody with the requisite binding specificity is used, the method or assay can be conducted in any suitable format, *i.e.*, the complex formed between the whole parathyroid hormone and the antibody can be assessed in any suitable way. For example, the complex can be assessed directly as in a sandwich assay format. In anther example, the complex can be assessed indirectly as in a competitive assay format. These various ways of assessing the complex are well know in the art. (Cruse et al., Illustrated Dictionary of Immunology, CRC Press, Second Ed., 2003, at pages 162 and 530) (Exhibit D).

In addition, step (c) of claim 10 recites "assessing a complex formed between said whole parathyroid hormone, if present in said sample, and said antibody, to measure physiological level of said whole parathyroid hormone in said mammalian sample." Therefore, the "assessing" step directly relates to the measurement of the level of the whole PTH in the sample.

The Examiner states that with respect to claim 17, the claim language "comprising" is allegedly vague and indefinite. The Examiner suggests using "consisting" instead since comprising is an open language and the recited antibody may also bind to the whole 1-84 PTH.

Applicant respectfully traverses this rejection. Claim 17, in the presently amended form, recites "the antibody specifically binds to an epitope comprised in PTH_{1-6}, PTH_{1-8}, PTH_{1-9}, PTH_{1-12}, or PTH_{1-15}." Therefore, claim 17 requires that the recited antibody must bind to an epitope comprised, *i.e.*, included, in the recited PTH peptide sequence. The use of "comprised" means that

it is possible that the recited antibody may bind to epitopes outside the recited PTH peptide sequence. But this does not render claim 17 indefinite because the binding specificity of the recited antibody is clearly defined by the epitope included in the recited PTH peptide sequence.

The Examiner states that with respect to claim 18, it is allegedly not clear whether the "at least four amino acids" are contiguous or simply randomly selected within the epitopes, such as human PTH_{1-8}, say amino acid 1 and 6-8. The Examiner also states that it is allegedly confusing because applicant further recites the binding between the antibody and the N-terminal sequence of whole PTH is dependent on the presence of amino acid residues 2-5 of the hPTH. The Examiner request Applicant to clarify.

Applicant respectfully traverses this rejection. Both linear and conformational epitopes are known in the art:

> Several categories of epitope have been defined for protein antigens, based on the proximity of the relevant amino acids in the primary structure of the protein (Fig. 14.3). The simplest case is the *linear* epitope, where all of the amino acids constituting the epitope are derived from a contiguous stretch of the polypeptide chain. However, many - perhaps most - epitopes on globular proteins involve amino acids from two or more stretches of polypeptide that are distant from one another in the primary structure. Such an epitope is referred to as *conformational* or *discontinuous*.

(Exhibit E, Rich et al., *Clinical Immunology Principles and Practice*, Second Ed., Mosby (2001) at 14.4.) As recognized by the Examiner, "at least four amino acids" in claim 18 can be part of a linear or a conformational epitope. And there is nothing unclear about this. hPTH 2-5 is an exemplary linear epitope of four amino acid residues in the N-terminus of hPTH.

The Examiner states that with respect to claim 22, it is allegedly not clear why the non-whole PTH fragments is between PTH_{3-84} and PTH_{34-84} since 3-84 is overlapped with the N-terminal which is within the whole PTH region.

Applicant respectfully traverses this rejection. A "peptide having an amino acid sequence from between PTH_{3-84} and PTH_{34-84}" recited in claim 22 is meant to encompass a group of C-terminal PTH fragments in which the N-terminal residue can start at any position among residues 3 to 34 of PTH and the C-terminal PTH fragments always end at residue 84 of PTH. To advance prosecution, claim 22 is amended to list the group of C-terminal PTH fragments.

The Examiner states that with respect to claim 33, it is allegedly not clear what is this PTH peptide, for instance, what is the metes and bounds. The Examiner states that with respect to claim 35, it is allegedly not clear what is the "mid-terminal PTH fragment," the "C-terminal PTH fragment" and the "N-terminal PTH fragment."

Applicant respectfully points out the "mid-terminal PTH fragment," the "C-terminal PTH fragment" and the "N-terminal PTH fragment" are defined in the present specification. (*See* the present specification at pages 14-15, paragraphs **[0068-0070]**.) The "PTH peptide" recited in claim 33 can be any of the "mid-terminal PTH fragment," the "C-terminal PTH fragment" and the "N-terminal PTH fragment."

The Examiner states that with respect to claim 81, it is not clear whether the recited unit is correct, i.e. pgm/ml. See Figure 5, the expression unit is pg/ml, not pgm/ml.

Applicant appreciates the Examiner's identification of this spelling error and has amended claim 81 per the Examiner's suggestion.

For all of the above reasons, Applicant respectfully requests withdrawal of all rejections under 35 U.S.C. 112, second paragraph.

Rejections under 35 U.S.C. §102

Slatopolsky

Claims 10-18, 22-39, 58 and 81 are rejected under 35 U.S.C. 102(b) as allegedly being anticipated by Slatopolsky et al., *Kidney Intl.*, 58:753-761 (2000) (Slatopolsky). Slatopolsky is alleged to teach a method of measuring a physiological level of whole parathyroid hormone in a mammalian sample. Slatopolsky is also alleged to teach obtaining uremic patients blood samples, and using an antibody recognizing only the first six amino acids of the parathyroid hormone (PTH), i.e. N-terminal sequence, which would not bind to the non-whole PTH fragments, to determine binding as the level of the whole PTH in the patient's sample (See page 753, left column, fist paragraph; page 754, right column, Methods).

Applicant respectfully traverses this rejection. The present application is a continuation-in-part of and claims priority of U.S. Patent Application No. 09/344,639, ('639 Application) filed on June 26, 1999, now U.S. Patent No. 6,743,590 (the '590 Patent) (Exhibit F). Many of the experiments in Slatopolsky that are relied upon by the Examiner are described in the '639 Application and the '590 Patent. For example, the assay method described at page 754, right column, of Slatopolsky is essentially the same as the method described at 5:65-6:23 of the '590 Patent. The assay principle illustrated in Figure 1 of Slatopolsky is identical to Figure 6 of the '590 Patent. The assay results shown in Figures 2, 3, 5 and 7 of Slatopolsky are the same or similar to the assay results shown in the Figures 10, 11, 12 and 5 of the '590 Patent, respectively.

Claims 10 and 59 find support in the '639 Application and are entitled to the filing date of '639 Application, June 26, 1999. Claims 10 and 59 are directed to a method and a kit for measuring a physiological level of whole parathyroid hormone in a mammalian sample using, *inter alia*, an isolated antibody that specifically binds to an N-terminal sequence of whole PTH and is capable of detecting said whole PTH at a physiological level in said mammalian sample, with a proviso that said isolated antibody avoids binding to a non-whole PTH fragment in said sample. A whole PTH immunoassay using an antibody with the requisite binding specificity is described in the

'639 Application and the '590 Patent. (*See* the '590 Patent at 5:36-6:36.) The '639 Application and the '590 Patent also teach that "one can either differentiate between parathyroid disease states and the normal state or monitor the effects of therapeutic treatment for parathyroid disease states by examining independently the value of either wPTH, PIN, or total PTH alone." (*See* the '590 Patent at 4:51-55; and 11:24-27.) The '639 Application and the '590 Patent further teach the use of whole PTH immunoassay for measuring a physiological level of whole PTH in a mammalian sample, *e.g.*, a human clinical sample. (*See* the '590 Patent at 8:20-12:17.)

Other additional features in Slatopolsky that are relied upon by the Examiner are also described in the '639 Application and the '590 Patent:

- With respect to claims 11-18,
    - the samples are from hyperparathyoid or renal transplant patients' blood - the '590 Patent at 1:63-2:4; 5:9-11; 8:20-12:17; and in Figure 8.
    - The antibody could be monoclonal or polyclonal antibody - the '590 Patent at 6:24-35.
    - The antibody specifically binds to an epitope of PTH_{1-6} - the '590 Patent at 5:65-6:15.
- With respect to claim 22-23,
    - the non-whole PTH fragment being PTH_{7-84} - the '590 Patent at 5:1-4[1]; SEQ ID NO:6 at columns 13-16; and in Figures 1, 5, 6 and 11.
- With respect to claim 24,
    - using sandwich or competitive assay to determine the PTH level - the '590 Patent at 5:38-50.

[1] The "(7-94) (SEQ ID NO:6))" at 5:3-4 is a typographic error. It should be "(7-84) (SEQ ID NO:6))."

- With respect to claims 25-30 and 33, using two antibodies, i.e. first for N-terminal PTH_{1-6} and the second for PTH_{7-84} which is a region other than the N-terminal, as capturing agents for whole PTH assay - the '590 Patent at 5:65-6:24.

- The assay kit (i.e. Scantibodies laboratories, Santee CA) provides solid surface and biotin-avidin linker for the attachment of antibodies - the '590 Patent at 5:65-6:24.

- With respect to claims 31-32, 81,

  - the level of parathyroid hormone in serum is around 344 pg/ml which is less than 4 pmol/L or within the range of 7 pg/ml to 39 pg/ml - the '590 Patent at 8:35-12:16.

- With respect to claim 34,

  - using antibody to measure PTH_{7-84} peptide (*See* Slatopolsky page 754, right column, Method) - The cited portion of Slatopolsky does not teach an antibody to measure PTH_{7-84} peptide.

- With respect to claim 35,

  - selecting two parameters, *e.g.*, whole PTH level and intact PTH level in comparison of normal and patient serum sample - the '590 Patent at 3:18-24; 4:35-44; and 8:35-12:16.

- With respect to claims 36-39,

  - using the comparison, i.e. ratio of whole PTH versus total PTH, as a monitoring tool to determine bone turnover related disorder or hyperparathyrodism - the '590 Patent at 3:18-24; 4:35-44; and 8:35-12:16.

- With respect to claim 58, the measurement of the level of whole PTH is useful for differentiating the normal PTH function and the hyperthyroidism - the '590 Patent at 4:50-54; and 8:35-12:16.

Therefore, in relation to Slatopolsky, all the rejected claims find support in the '639 Application and are entitled to the filing date of '639 Application, June 26, 1999. Since Slatopolsky was published in 2000, Slatopolsky is not prior art to the rejected claims.

Gao

Claims 10-18, 22-32, 58 and 81 are rejected under 35 U.S.C. 102(b) as allegedly being anticipated by Gao et al., *J. Bone Mineral Res.*, 16:605-614 (2001) (Gao).

Applicant respectfully traverses this rejection. As discussed above in connection with Slatopolsky, the rejected claims are entitled to the June 26, 1999 filing date. Since Gao was published in 2001, Gao is not prior art to the rejected claims.

For all of the above reasons, Applicant respectfully requests withdrawal of all rejections under 35 U.S.C. 102.

CONCLUSION

In view of the above, each of the presently pending claims in this application is believed to be in immediate condition for allowance. Accordingly, the Examiner is respectfully requested to withdraw the outstanding rejection of the claims and to pass this application to issue. If it is determined that a telephone conference would expedite the prosecution of this application, the Examiner is invited to telephone the undersigned at the number given below.

In the event the U.S. Patent and Trademark office determines that an extension and/or other relief is required, applicant petitions for any required relief including extensions of time and authorizes the Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to Deposit Account No. 03-1952 referencing docket no. 532212000623. However, the Commissioner is not authorized to charge the cost of the issue fee to the Deposit Account.

Dated: March 28, 2005

Respectfully submitted,

By_____

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